Management of diabetic nephropathy

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Diabetic nephropathy is the single most common cause of end-stage renal disease in the western world and is associated with greatly increased cardiovascular morbidity and mortality. With the rising prevalence of type 2 disease it has come to pose a heavy burden on healthcare systems worldwide. Investment in fundamental and clinical research has yielded strategies that can reduce the risk of diabetic renal disease and slow its progression.

THE STAGES OF DIABETIC NEPHROPATHY

Type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes are aetiologically and epidemiologically distinct conditions affecting different segments of the population. Nevertheless, no major difference has been identified between the nephropathies seen in these conditions, either pathophysiologically or in terms of management. They can thus be conveniently considered together. It should be remembered, however, that patients with type 2 diabetes tend to be older and more hypertensive, and thus more likely to have concomitant hypertensive and renovascular disease.

The association of proteinuria with diabetes was first recognized in the eighteenth century but it was Kimmelstiel and Wilson[1] in 1936 who defined the condition by describing the lesions of nodular glomerulosclerosis and the association with proteinuria and hypertension in type 2 diabetes. These features represent a late stage in the progression of the condition. Subsequent work, mainly on type 1 diabetes, led to the definition of several distinct phases in the evolution[2] of the disease.

Hyperfiltration

Hyperfiltration, characterized by renal enlargement, intrarenal hypertension and high glomerular filtration rate (GFR), may be seen early in the course of diabetes[3]. These haemodynamic phenomena, although partly reversible by glycaemic and blood pressure control, have been linked with the development of microalbuminuria[4,5]. Early microalbuminuria is usually associated with a raised GFR, and a normal GFR in this context may indicate that renal function has already been lost.

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Silent phase

Very few patients develop microalbuminuria during the first ten years of their diabetes (type 2 diabetes may of course remain undiagnosed for many years and present with advanced disease). During this so-called silent phase early histological abnormalities in the kidney may be seen, including glomerular hypertrophy and subtle thickening of the glomerular basement membrane, best seen by electronmicroscopy.

Microalbuminuria

The normal urinary protein excretion rate is up to 300 mg/24 h, of which about 10% is albumin, equivalent to an albumin excretion rate of 20 μg/min. Albumin excretion rates of 20–200 μg/min, equivalent to a urine albumin creatinine ratio (ACR) of 10–25 mg/mmol, are defined as microalbuminuria (also called incipient nephropathy) as these levels are not detectable by conventional urine dipstick analysis (Table 1). The onset of microalbuminuria is highly significant since its presence predicts the development of overt renal disease in both type 1 and type 2 diabetes[6,7]. Furthermore, microalbuminuria is associated with an increased risk of cardiovascular and microvascular complications as well as an increase in all-cause mortality, especially in type 2 diabetes[8] (Box 1). Renal histology at this stage reveals typical glomerulosclerosis. Once microalbuminuria is established the trend is one of increasing proteinuria until overt nephropathy develops.

Overt nephropathy

Albumin excretion rates above 200 μg/min or 300 mg/day (equivalent to an ACR of $>$25 mg/mmol) are dipstick positive and defined as overt nephropathy. This is usually associated with a relentless loss of GFR (by 1–24 mL/min per year) until end-stage renal failure necessitates dialysis or renal transplantation. The rate of progression of microalbuminuria and overt nephropathy is heavily influenced by blood pressure control, diabetic control and the use of angiotensin converting enzyme (ACE) inhibitors—strategies that form the cornerstone of management.

Table 1 **Definitions in diabetic renal disease**

	Normal	*Microalbuminuria (incipient nephropathy)*	*Clinical 'overt' nephropathy*	*Units*
24 hour urinary albumin	<30	30–300	>300	mg/day
Urine albumin excretion rate	<20	20–200	>200	μg/min
Urine albumin/creatinine ratio	<2.5 M <3.5 F	10–25	>25	mg/mmol

RISK FACTORS FOR DEVELOPMENT AND PROGRESSION OF DIABETIC NEPHROPATHY

Before the widespread aggressive treatment of blood pressure and hyperglycaemia, between 25% and 40% of both type 1 and type 2 patients developed diabetic nephropathy over the course of 25 years[9–11] and risk factors that differentiate this subgroup from patients who maintain normal renal function are systemic hypertension, glycaemic control, gender (M>F), genetic factors, hyperlipidaemia, dietary protein intake and smoking.

Blood pressure

Hypertension is much more common amongst diabetic patients than in the general population and has been identified as a major risk factor for both macrovascular and microvascular complications including diabetic nephropathy. Total cardiovascular mortality in diabetes is strongly associated with raised blood pressure, particularly in type 2 disease.

Hypertension is strongly associated with insulin resistance, even in the absence of diabetes, and some 40–70% of type 2 patients will become hypertensive during their disease[12]. Only 25% of patients with type 1 diabetes are hypertensive and many of these will already have microalbuminuria or overt nephropathy[13]. Nevertheless, in both type 1 and type 2 diabetes with overt nephropathy the rate of decline of renal function correlates strongly with hypertension[14,15], and in microalbuminuric patients hypertension correlates with the degree of albuminuria[16]. In both these situations antihypertensive therapy is beneficial. Furthermore in normoalbuminuric type 1 diabetes small increases in blood pressure have been correlated with the subsequent development of microalbuminuria[17]. There can therefore now be little doubt that a raised blood pressure is a risk factor for the development and progression of diabetic nephropathy as well as a potent risk factor for cardiovascular morbidity and mortality.

Box 1 **Associations with microalbuminuria**

- Development of overt nephropathy and end-stage renal disease
- Increased cardiovascular risk
- Blood pressure changes:
  - Loss of nocturnal dip in BP
  - Rise in BP (mean 3 mmHg per year)
- Other microvascular complications of diabetes:
  - Proliferative diabetic retinopathy
  - Macular oedema
  - Neuropathy
- Dyslipidaemia
- Insulin resistance

Glycaemic control

Type 1 and type 2 diabetes have in common the state of chronic hyperglycaemia, and glucose-dependent processes are likely to be involved in the pathogenesis of diabetic complications, including nephropathy. Glucose-induced tissue injury may be mediated by the generation of advanced glycated proteins or via other mechanisms such as the polyol pathway, both of which have been implicated in nephropathy[18]. Consistent with this hypothesis are observational studies correlating haemoglobin A1c (HbA1c) concentration with the development and progression of microalbuminuria and overt nephropathy[17].

Proteinuria

Proteinuria is generally regarded as a marker for the degree of glomerular damage: the level of proteinuria correlates well with the prognosis for renal function, and interventions that retard the progression of diabetic renal disease also reduce proteinuria. However, we do not yet know whether the flux of protein across the glomerular basement membrane is causally implicated in the evolution of diabetic renal disease or simply reflects glomerular damage[19].

Genetic factors

Genetic factors are likely to be important in diabetic nephropathy. Recent interest has focused on genes of the

renin angiotensin system, which are known to be highly polymorphic and have been extensively studied in relation to cardiovascular disease. An insertion(I)/deletion(D) polymorphism in the ACE gene has been identified that is strongly associated with raised circulating ACE levels and with increased risk of coronary heart disease in non-diabetic individuals. Some studies have found the DD genotype to be associated with an increased risk of diabetic nephropathy and a rapid decline of GFR in both type 1 and type 2 diabetes[20]. The clinical implications have yet to be explored. Other genetic loci that may be involved include the sodium–lithium exchanger and the sodium–hydrogen antiporter genes.

Hyperlipidaemia

Hyperlipidaemia is common in both type 1 and type 2 diabetes. Raised plasma triglycerides and low levels of high-density liproproteins (HDL) have been correlated with the development of diabetic nephropathy as well as with cardiovascular diabetic complications[9,21,22]. Triglyceride and cholesterol reduction, although important in reducing cardiovascular risk, has not been found to alter the progression of renal disease and the importance of hyperlipidaemia remains to be established in this respect.

Others

Other risk factors for diabetic nephropathy include smoking[23], dietary protein intake, levels of circulating von Willebrand factor and other plasma proteins, the presence of other diabetic complications (notably retinopathy), and non-attendance at follow-up clinics[24].

SCREENING FOR DIABETIC NEPHROPATHY

Diabetic patients with microalbuminuria are at high risk for the development of overt nephropathy and cardiovascular complications. The justification for screening is that identification of this cohort of patients allows aggressive intervention with a view to prevention.

Microalbuminuria

Several methods can be used for detection of microalbuminuria. The urinary albumin/creatinine ratio (ACR) can be determined from a random, or preferably early-morning, urine sample. This is often the easiest test in the setting of primary care and provides a practical screening method less prone to patient error than timed collection[25,26]. The albumin excretion rate (AER) is more precise and can be measured formally from any timed collection, most commonly overnight (8 hours)—which is technically easier for the patient than a 24-hour collection. Recently developed urine dipstick assays provide a useful initial screening test that can be performed in the surgery if assays for microalbuminuria are not readily available. However, they are subject to error from alterations in urine concentration and all positive tests should be confirmed by more specific methods.

Box 2 **Confounding factors in screening for microalbuminuria**

False positive	Diurnal variation
	Urinary tract infection
	Acute illness (i.e. fever)
	Congestive cardiac failure
	Uncontrolled hypertension
	Hyperglycaemia
	Exercise
False negative	Diuresis
	Dilution

Microalbuminuria should be diagnosed on the basis of three positive tests—ACR, AER or a combination of the two—over a 3–6 month period. Albumin excretion can vary by as much as 40% and physicians should be aware of potential confounding factors (Box 2) and non-diabetic causes of renal impairment and proteinuria.

Because microalbuminuria rarely occurs within the first 5–10 years in type 1 diabetes or before puberty, screening should begin with onset of puberty or after 5 years' disease duration. In type 2 diabetes, where the precise onset of the disease cannot be dated, screening should begin at diagnosis[27]. Annual screening is generally recommended though some groups advocate more frequent testing[28]. Once microalbuminuria has been identified the patient should have measurements every 3–6 months.

Further investigations

When microalbuminuria has been confirmed, serum creatinine, urea and electrolytes should be measured at baseline and then yearly or half-yearly. Haematuria should also be tested for. It is helpful to monitor GFR annually. Isotopic GFR measurements may not be readily available and are rarely used in routine practice. Creatinine clearance approximates to GFR and can be measured by 24-hour urine collection or calculated from serum creatinine[29].

Risk factors associated with the progression of renal disease and/or the development of coronary heart disease (CHD) should be identified early and regular assessment of blood pressure is mandatory. Lipid levels should be checked at baseline and yearly or half-yearly—see Management.

Box 3 **Factors associated with non-diabetic renal disease in diabetic patients**

- Absence of retinopathy
- Sudden increase in proteinuria
- Early onset of nephrotic syndrome
- Sudden decline in renal function
- Haematuria
- Atypical biochemical/serological abnormalities
  (e.g. hypercalcaemia suggestive of myeloma; raised C-reactive protein or erythrocyte sedimentation rate)

Non-diabetic renal disease

Some groups have proposed a high rate of non-diabetic renal disease in type 2 diabetes but there is no conclusive evidence that complicating renal disease is more frequent in this group of patients than in the background population[30]. Most patients with diabetes and renal impairment will not require a renal biopsy. Certain factors raise the suspicion of a non-diabetic renal diagnosis and referral to a renal physician may then be required (Box 3).

MANAGEMENT

The risk of cardiovascular death in diabetic patients with microalbuminuria is some 7–40 times that of an age-matched general population; in normoalbuminuric diabetes it is 2.5. Microalbuminuria can thus be considered an indicator of an ongoing and generalized disease process affecting the whole of the cardiovascular system. Management of the patient with diabetic nephropathy must therefore focus on all cardiovascular risk factors as well as specifically on measures to retard the progression of renal disease. There is considerable overlap between these two aims (Figure 1).

Hypertension

The beneficial effect of lowering blood pressure, on both progression of renal disease and overall cardiovascular mortality, is now so well established that monitoring and control of blood pressure has become a major component of diabetic care. Current debates centre mainly on the choice of antihypertensive agents and on blood pressure targets.

The benefit of antihypertensive therapy on declining renal function was first demonstrated in small studies of type 1 diabetes. Mogensen[31] reduced the mean blood pressure of a group of type 1 diabetic patients with overt nephropathy from 163/103 to 144/95 mmHg and reported a drop in the monthly decline in GFR from 1.23 to 0.49 mL/min. A larger prospective study in similar patients[32,33] demonstrated a decline in the rate of loss of GFR from 0.94 to 0.29 mL/min per month during the first three years of effective antihypertensive treatment and 0.10 mL/min per month over the subsequent 10 years. This was associated with a 50% reduction in albuminuria and an anticipated increase in renal survival from 7 to more than 20 years. Total mortality and progression to end-stage renal disease are also substantially lower in treated than in untreated hypertensive type 1 diabetic patients with renal impairment[34].

In both type 1 and type 2 diabetic patients with microalbuminuria, blood pressure reduction also reduces or stabilizes AER[35,36] and retards the rate of progression to overt nephropathy.

The overall cardiovascular benefit of intensive control of blood pressure was illustrated by several recent studies. The United Kingdom Prospective Diabetes Study (UKPDS)[37] compared intensive with less intensive blood pressure control in type 2 diabetes, achieving a mean blood pressure of 144/82 and 154/87 Hg in the two groups, respectively. Intensive control resulted in a 32% lower mortality, predominantly from cardiovascular disease, and a reduction in microvascular complications including the development of microalbuminuria. The Hypertension Optimal Treatment (HOT) trial[38], which included a subset of mainly type 2 diabetic patients, compared three intensities of blood pressure control. Target blood pressures were diastolic $\leqslant 90$, $\leqslant 85$ and $\leqslant 80$ mmHg while achieved blood pressures were 144/85, 141/83 and 140/81 mmHg respectively. Despite the small differences in achieved diastolic pressure, major cardiovascular events in the $\leqslant 80$ mmHg diabetic subset were only half those in the $\leqslant 90$ mmHg group.

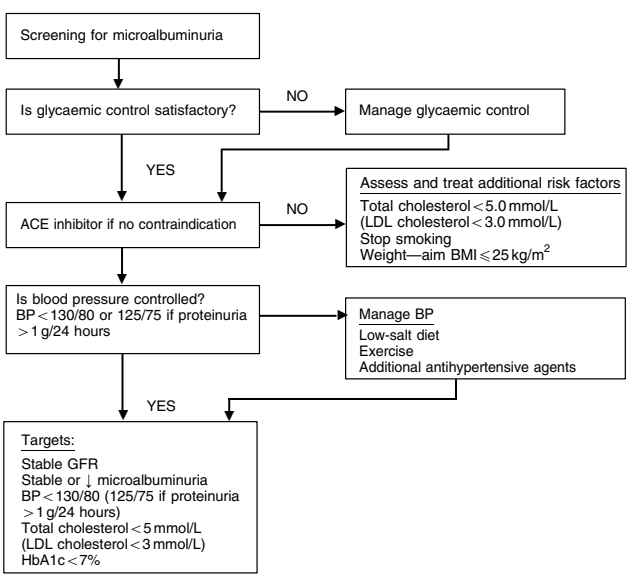

Figure 1 **Flow chart for management of diabetic nephropathy**

Blood pressure targets

Although the level of blood pressure below which further benefit would not be seen has yet to be firmly defined, the British Hypertension Society[39] has recommended initiating therapy in diabetic patients with blood pressure >140/90 mmHg and a target blood pressure of <140/80, or <125/75 mmHg in type 1 diabetic patients with >1 g/day of proteinuria. The Joint British Recommendations on the Prevention of Coronary Heart Disease in Clinical Practice[40] suggest maintaining blood pressure <130/80 or <125/75 in type 1 diabetes with >1 g/day of proteinuria. The US Joint National Committee on the detection, evaluation and treatment of high blood pressure[41] has recommended keeping blood pressure in diabetic patients below 130/85 mmHg. However, both the UKPDS and the HOT trial have illustrated the difficulty in achieving such ambitious targets, which require multiple antihypertensive therapy and good adherence to treatment. In the UKPDS, for example, 27% of patients in the tight blood pressure control group were prescribed three or more antihypertensive agents but 44% still had blood pressures of >150/85 mmHg at the end of the study period. Isolated systolic hypertension, reflecting reduced vascular compliance, is commonly seen in elderly type 2 diabetic patients. Although difficult to achieve, the benefits of even small reductions in systolic hypertension are established[42] and this condition should be actively treated.

In all diabetic patients blood pressure should be monitored at least 6-monthly, and when microalbuminuria develops at least 3-monthly. Instructing patients in self-measurement of blood pressure can be helpful in some circumstances. Borderline or inconsistent readings can be investigated with 24-hour ambulatory blood pressure measurement, but interpretation can be difficult and the utility of this method in clinical practice has yet to be defined.

ACE inhibitors

Although blood pressure reduction with any of the standard antihypertensive agents (β-blockers, diuretics, dihydropyridine calcium antagonists, α-blockers) is beneficial, ACE inhibitors exert a renoprotective effect beyond their antihypertensive properties in some circumstances. A combined analysis of two large studies of captopril versus placebo in microalbuminuric type 1 diabetes with controlled hypertension suggested a 63% reduction in progression to overt proteinuria over 2 years along with a decline in albumin excretion rate[43]. In type 1 diabetic patients with overt nephropathy captopril was associated with a substantial reduction in the rate of decline in renal function as well as a 50% reduction in death and end-stage renal disease over a four-year follow-up[44]. However, the preferential use of ACE inhibitors is not supported in type 1 diabetes without microalbuminuria[45].

In type 2 diabetes the evidence for the superiority of ACE inhibitors is less clear. In type 2 patients with microalbuminuria, ACE inhibition has stabilized AER and renal function in some studies[46] whereas others (including UKPDS) support the notion that blood pressure reduction *per se* is more important than the agent used. In the diabetic arm of the Heart Outcomes Prevention Evaluation (HOPE) study[47], which compared an ACE inhibitor with placebo in a mixed diabetic population (98% type 2) with controlled blood pressure and with at least one other cardiovascular risk factor, the incidence of myocardial infarction, stroke or cardiovascular death was 25% lower and the progression of microalbuminuria was slowed in the ACE inhibitor group.

In the light of this evidence and their favourable side-effect profile, ACE inhibitors should now be the first-line antihypertensive agent in both type 1 and type 2 diabetes. ACE inhibition is also indicated in non-hypertensive type 1 and type 2 diabetic patients with microalbuminuria or overt nephropathy[48], the dose being increased until AER falls into the normal range or hypotension develops. The main side-effect of ACE inhibitors is cough, which may limit use. Although up to 60% of type 2 diabetic patients have radiological evidence of atheromatous renovascular disease, acute reduction of GFR is seldom observed with ACE inhibitors; this effect, and hyperkalaemia, should be screened for by measuring serum creatinine and electrolytes shortly after the start of treatment and 6-monthly thereafter. In the presence of peripheral vascular disease, ischaemic heart disease or congestive cardiac failure it is prudent to start ACE inhibitors at a low dose given at night, and temporarily to suspend the use of loop diuretics. Concomitant use of ACE inhibitors and potassium-sparing diuretics should always be avoided.

Angiotensin II receptor blockers offer a theoretical alternative to ACE inhibitors. They are effective antihypertensives but have not been validated in large outcome studies and should be reserved for patients who do not tolerate ACE inhibition. Other antihypertensive drugs may be added according to standard protocols[39]. In general, once-daily preparations with long intrinsic half-lives are preferable in terms of adherence to treatment and the consequences of missing a dose.

A low-salt diet is a non-pharmacological measure commonly advocated, but the evidence is not clear-cut and patients are not receptive to salt restriction at the level likely to be effective.

Glycaemic control

Good glycaemic control reduces the risk of microalbuminuria and overt renal disease[49–51] though there is no clear evidence that it affects the progression of nephropathy in diabetes complicated by microalbuminuria[50,52]. The benefits on the progression of both retinopathy and neuropathy are well documented[50,51]. In view of this and the potential benefits in both renal and cardiovascular disease the British and US recommendations are to establish and maintain tight blood glucose control, with a target HbA1c of $\leqslant 7\%$[27,40].

Lipids

Dyslipidaemia is a risk factor for both development[53] and progression[54,55] of renal dysfunction in primary renal disease. There are no primary prevention studies to show whether intervention with lipid-lowering therapy significantly affects the rate of decline of renal function in either diabetic or non-diabetic renal disease; nevertheless there are compelling reasons for aggressive management of dyslipidaemia in patients with microalbuminuria or overt nephropathy, and a full lipid profile should be checked at baseline and then yearly or half-yearly in these patients. As previously discussed, this group of patients are at greatly increased risk of cardiovascular disease. Several observational studies have pointed to both total cholesterol and triglyceride concentrations as significant predictors of coronary heart disease in type 2 diabetes[56–58]. In the UKPDS[50], high levels of LDL cholesterol or total cholesterol, and low HDL cholesterol, were major independent risk factors for coronary artery disease. High triglycerides were not an independent risk factor.

The benefits of lipid lowering in diabetic patients with proven coronary heart disease are certain. In two large secondary prevention studies, the Scandinavian Simvastatin Survival Study[59] and the Cholesterol and Recurrent Events Trial[60,61], diabetic subgroups have been looked at and the benefit of statins in reducing coronary events were equal to if not greater than those in the total group.

Studies are underway to test the role of both fibrates and statins in the *primary* prevention of cardiovascular disease in the diabetic population. One primary prevention study with gemfibrozil, the Helsinki Heart Study[62], has shown a non-significant reduction in coronary events in a small diabetic subgroup. Primary prevention studies in non-diabetic individuals have focused mainly on hypercholesterolaemia in middle-aged men[63], in whom statins seem to reduce not only coronary events but also overall mortality.

Diabetic patients with CHD have poor outcomes[64]. This fact coupled with the high cardiovascular risk in diabetic patients with nephropathy identifies a group of patients very likely to benefit from early and aggressive treatment of dyslipidaemia before the onset of clinical CHD.

Improvement of glycaemic control reduces hypertriglyceridaemia but may have only modest effects on HDL and LDL levels; thus pharmacological intervention is usually required. Current recommendations in the UK are to maintain total cholesterol < 5.0 mmol/L (LDL cholesterol < 3.0 mmol/L)[40]. Statins are the drugs of choice in patients with established CHD. Information needed from future trials includes target levels, first-choice agents in primary prevention and the value of lipid lowering in young diabetic patients with nephropathy.

Low-protein diet

Two meta-analyses have shown a beneficial effect of dietary protein restriction on the progression of diabetic nephropathy in type 1 diabetes[65,66]. It remains unclear what level of protein restriction should be used, how acceptable this will prove to patients and how this will relate to treatment adherence in the setting of routine primary care. Long-term prospective studies are required to look at these issues in both type 1 and type 2 diabetes.

Aspirin

A meta-analysis of 145 prospective trials of antiplatelet therapy has confirmed the benefit of secondary prevention with aspirin treatment in patients with established atherosclerotic disease, with similar benefits seen in diabetic and non-diabetic patients[6,7]. Two primary prevention studies, the General Practice Research Framework Thrombosis Prevention Trial[68] and the US Physicians Health Study[69], have shown a reduction in non-fatal events in men at increased risk of coronary heart disease treated with aspirin. In the US Physicians study fatal events were also reduced, and a subgroup analysis in the diabetic group showed a reduction in myocardial infarction from 10.1% in the placebo group to 4.0% in the aspirin group. People aged 50 or more seemed to benefit most. Current recommendations on prevention of coronary heart disease[40] suggest aspirin treatment (75 mg daily) in individuals aged over 50 years whose hypertension, if present, is controlled and who are at high risk (absolute CHD risk $\geqslant 15\%$ per 10 years). The high cardiovascular risk in patients with microalbuminuria or overt nephropathy argues strongly for the use of aspirin as a primary prevention strategy in some of these patients, but there are no data on the use of aspirin in younger diabetic patients (< 30 years old).

Lifestyle targets

Stopping smoking, increasing aerobic exercise and cutting excessive alcohol consumption are important lifestyle targets. Aerobic exercise in particular has been shown to improve insulin sensitivity and reduce cardiovascular risk in type 2 diabetes. A body mass index of $<25\,kg/m^2$ with no central obesity is desirable but often very hard to achieve.

CONCLUSION

Diabetic end-stage renal disease is a devastating condition that can be avoided in some cases and substantially delayed in many. The detection of microalbuminuria identifies a subgroup of patients with a high risk of cardiovascular morbidity and mortality as well as diabetic renal disease and aggressive management of these patients can greatly improve their outlook. Physicians who care for diabetic patients must therefore undertake careful screening and implement effective long-term regimens for control of hypertension and glycaemia. Nor must cardiovascular risk factors such as smoking and hyperlipidaemia be neglected. The cost and difficulty of achieving these goals can be great, but so too are the potential benefits.

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